Author's response to reviews

Title: Superficial and deep sternal wound infection after more than 9000 coronary artery bypass graft (CABG): incidence, risk factors and mortality

Authors:
Abbas Salehi Omran (abbasomran1385@yahoo.com)
Abbasali Karimi (akarimi@tums.ac.ir)
S.Hossein Ahmadi (shossein1330@yahoo.com)
Setareh Davoodi (abbasomran1385@yahoo.com)
Mehrab Marzban (mehrabmarzban@yahoo.com)
Namvar Movahedi (nmovahedi@yahoo.com)
Kyomars Abbasi (QuoAB@yahoo.com)
Mohammad Ali Boroumand (borumand@tehranheartcenter.org)
Saeed Davoodi (sdavoodi@yahoo.com)
Naghmeh Moshtaghi (naghmeh_moshtaghi@yahoo.com)

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I would like to thank you for your helpful comments. All of the changes that have been made are listed below and also are found in my revised manuscript as highlight.

Reviewer: Kevin Garey

1. Abstract, conclusion: The last sentence is deleted as your suggestion.
2. Background: line 8: It is changed as follow: According to the proposed centers for disease control and prevention classification (CDC), infection of surgical wounds of sternotomies should be considered as superficial if only the skin and subcutaneous tissue is involved; deep when the infection reaches the sternum but does not involve it and as organ space infections when sternal osteomyelitis or mediastinitis occur. CDC classification enables a better comparison among scientific works. For the sake of consistency in comparing data from various reports SWI sub divided to two groups: (A) superficial sternal wound infection: wound infection confirmed to the subcutaneous tissue and (B) deep SWI (mediastinitis) wound infection: wound infection associated with sternal osteomyelitis with or without infected retrosternal space [3].

3. Background, third paragraph: the SSI rate of 2% was illustrated with reference No.13 as your suggestion.

4. Background, fourth paragraph: The Oakley classification was described as follow: In our study; we also classified our cases of deep SWI according to Oakley classification of mediastinitis. Deep sternal wound infections, or mediastinitis, are classified into four subtypes based on the time of first presentation, the presence or absence of risk factors, and whether previous attempts at treating the condition have failed [3].

5. Methods, paragraph 2: the method used to identify patients with SSI should be expanded: any sign of SWI evaluated promptly.

6. Methods, paragraph 2, and last sentence: it is changed as follow: Immediately after suspicion of SWI, antibiotics were administrated and surgical intervention was made.


8. Statistical methods: this section was changed as follow: Numerical variables were presented as mean +/- SD, and categorized variables were summarized by percentages. Missing data were present in less than 2.5% of records. Continuous variables were compared using the student's test or nonparametric Mann-Whitney U test whenever the data did not appear to have normal distributions, and categorical variables were compared using the chi-square or Fisher's exact test. Power analysis showed that was about 69% chance of detecting a significance difference using a two-sided test with significance level=0.05.
Multivariate forward stepwise logistic regression model for risk factors predicting SWI was constructed. Variables were included into the multivariate model if the p value was found to be less than or equal to 0.15 in the univariate analysis. The associations of independent predictors with SWI in the final model were expressed as odds ratios (OR) with 95% CIs. Model discrimination was measured using the c statistic, which is equal to the area under the ROC curve. Model calibration was estimated using the Hosmer-Lemeshow (HL) goodness-of-fit statistic (higher P values imply that the model fits the observed data better). For the statistical analysis, the statistical software SPSS version 13.0 for windows (SPSS Inc., Chicago, IL) and the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) were used. All p values were 2-tailed, with statistical significance defined by pGBP0.05.

9. Results: in this section "about", "and this difference was significant" was deleted as your suggestion. SD presented with mean values as your suggestion.

10. Results second paragraph: Do the authors feel that" mortality rates for SWI in general were similar to mortality rates for mediastinitis" could have been due to misclassification of SWI?
In my opinion, it seems that SWI mortality is related to infectious and non infectious causes.

11. Is there any explanation for a very low incidence of infections caused by S.epidermidis or other coagulase negative Staphylococcus?
This result was according to lab data.

12. Discussion, last paragraph: we delete the sentence of "early diagnosis and good follow-up" as your suggestion. This sentence was changed as follow: We think low rate of SWI in our center is due to meticulous control of pre operative, operative and post operative care of the patients.

13. Conclusion: the last sentence was changed as follow: We think low rate of SWI in our center is due to meticulous control of pre operative, operative and post operative care of the patients.


According to comments of reviewer 1 and 2 we put table 1,2 and 3 together into one table as follow: Table 1: Pre-intra-and postoperative characteristics among patients with and without SWI*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1**</th>
<th>Group 2**</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean+/−SD)</td>
<td>58.5+/−9.76 60.1+/−8.78 0.173</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (mean+/−SD)</td>
<td>27.0+/−4.00 28.3+/−4.05 0.630</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female %</td>
<td>25.5 52.3 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking %</td>
<td>39.5 34.1 0.467</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes %</td>
<td>33.7 59.1 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia %</td>
<td>61.0 65.9 0.508</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension %</td>
<td>49.7 90.9 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD %</td>
<td>1.8 2.8 0.666</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of preoperative hospital stay (days) (mean+/−SD)</td>
<td>8.2+/−4.94 9.4+/−6.16 0.098</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS (Functional class) (mean+/−SD)</td>
<td>2.1+/−0.88 2.6+/−0.71 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (mean+/−SD)</td>
<td>49.1+/−10.23 50.7+/−11.21 0.260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft number (mean+/−SD)</td>
<td>3.60+/−0.91 3.61+/−1.03 0.928</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross clamp time (minute) (mean+/−SD)</td>
<td>42.46+/−41.56 45.09+/−16.45 0.686</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfusion time (minute) (mean+/−SD)</td>
<td>70.13+/−26.01 75.26+/−23.58 0.207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-exploration for bleeding 1%</td>
<td>13.6% &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation time (hours) (mean+/−SD)</td>
<td>8.91+/−13.64 54.13+/−172.10 &lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Body mass index, BMI; Peripheral vascular disease, PVD; Canadian Cardiovascular Society classification, CCS; left ventricular ejection fraction, LVEF
** Group 1: without sternal wound infection , Group 2: with sternal wound infection

15. We delete table 5 and 6 as your suggestion.
16. In table 7all re-exploration for bleeding in our cases was the post CABG complication and did not occur after SWI.

Minor Essential Revisions:

1. Abstract; results section: The sentence that begins with "Female gender..." Was changed as follow: Female gender, pre operative hypertension, high functional class, diabetes mellitus, BMI (body mass index), prolonged intubation time (more than 48h) and re-exploration for bleeding were significant risk
factors for developing SWI (p[less than or equal to]0.05) in univariate analysis.

2. Results second paragraph was changed as follow: In multivariate analysis, hypertension (OR=10.7) re-exploration (OR=13.4), and female gender (OR=2.7) were identified as significant predictors of SWI (p<0.05 for all).

Reviewer: Orjan Friberg

1. Background paragraph 2and 3: It is changed as your suggestion as follow: According to the proposed centers for disease control and prevention classification (CDC), infection of surgical wounds of sternotomies should be considered as superficial if only the skin and subcutaneous tissue is involved; deep when the infection reaches the sternum but does not involve it and as organ space infections when sternal osteomyelitis or mediastinitis occur. CDC classification enables a better comparison among scientific works. For the sake of consistency in comparing data from various reports SWI sub divided to two groups: (A) superficial sternal wound infection: wound infection confirmed to the subcutaneous tissue and (B) deep SWI (mediastinitis) wound infection: wound infection associated with sternal osteomyelitis with or without infected retrosternal space [3].

The overall incidence of deep sternal wound infection (mediastinitis) varies from 0.4% to 5% independent of type of surgery and this is accompanied by a high mortality rate. The incidence of superficial surgical site infections (SSSI) in sternotomies should be similar to any clean surgical procedure, that is, approximately 2%. However, the infection rate reaches three times this value among heart disease patients, since these patients face a higher number of risk factors than the population in general [2,3,13].

2. Methods section: in paragraph 1, the second sentence was changed as follow: Our study was a retrospective analysis of prospectively collected data.

3. In our center database was entered by general practitioner. All data of mediastinitis was found of database of surgery and lab data. we are sure there is no data missing in SWI group.

4. Were all patients followed, and contacted after discharge? If so, for how long were the patients followed? If not, how, when and by whom was the diagnosis of SWI made and then entered in the database?

In our study early follow-up (in-hospital follow-up) was simple and after that time patients came to follow-up clinic every 6 months. Among these patients SWI patients referred to clinic of surgery.

5. As your suggestion we considered CDC classification in background section.

6. Brief description of the classification according to el Oakley was defined in the last paragraph of background section as follow: In our study; we also classified our cases of deep SWI according to Oakley classification of mediastinitis. Deep sternal wound infections, or mediastinitis, are classified into four subtypes based on the time of first presentation, the presence or absence of risk factors, and whether previous attempts at treating the condition have failed [3].

7. in our study in-hospital mortality: it means mortality during 30 days after operation.

8. Antibiotic prophylaxis was started 30 minutes before surgery and repeated every 3 hours. Aminoglycosides did not repeat at the same intervals. The doses in gram of each of the antibiotics should be given: All the prophylactic antibiotics were administered as a single dose 30 minutes before surgery and continued up to 48 hours after CABG at 3-hour intervals. Cefazolin was given 1 gr. every 8 hours; those with a weight>80 received 2 gr. Gentamycin and Amikacin were dispensed 1mg/kg/dose and 5mg/kg/dose, respectively.

9. Statistical methods: Exactly which factors were entered in the multivariable analysis? All with a p-value less than .05? Was intubation time entered (or was it considered a consequence of SWI rather that risk factor for SWI)? (I suppose mortality was not entered?) Were possible statistical interactions between factors tested? Was any alternative statistical analysis used (if e.g. a backward stepwise analysis would give the same final model, it would indicate a robust model)? Hosmer-Lemeshow test? We did statistical interactions between factors, but there were not any interactions between factors. Multivariate forward stepwise logistic regression model for risk factors predicting SWI was constructed. Variables were included into the multivariate model if the p value was found to be less than or equal to 0.15 in the univariate analysis. The associations of independent predictors with SWI in the final model were expressed as odds ratios (OR) with 95% CIs. Model discrimination was measured using the c statistic, which is equal to the area under the ROC curve. Model calibration was estimated using the Hosmer-Lemeshow (HL) goodness-of-fit statistic (higher P values imply that the model fit the observed data better). For the statistical analysis, the statistical software SPSS version 13.0 for windows (SPSS Inc., Chicago, IL) and the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) were used. All p values were 2-tailed, with statistical significance defined by pGBP0.05.

10. in result section: Eight of the SWIs belonged to El Oakley type IVb. How did the authors handle list? These patients received one course of antibiotic therapy but not responded to it.

11. Table 1, 2 and 3 put together into one table (summarizing potential pre-intra- and postoperative risk
factors).
12. BMI: It was incorrect; we considered 2-tailed instead of equality of variance by mistake.
13. Table 4, 5 and 6 were omitted.
14. In all tables the same number of one decimal was given.
15. Discussion: The finding of preoperative hypertension as an independent, highly significant risk factor for SWI was somewhat surprising. Do the authors think this reflects a true causal relationship and if so, what might be the mechanism? Maybe HTN change wound healing process.
Reviewer: Ioannis Toumpoulis
1. What is the power of the study to detect differences among the groups analyzed? Do the authors think that their study has sufficient power? Power analysis showed that was about 69% chance of detecting a significance difference using a two-sided test with significance level=0.05.
2. I miss other important potential risk factors from this study (i.e. renal failure, sepsis, endocarditis, COPD and emergent operation). What do the authors think of their impact on SWI? In our study none of the patients had these risk factors but other studies showed importance of these factors.
3. What is the discrimination ability and the calibration of the multivariate logistic regression model? Model discrimination was measured using the c statistic, which is equal to the area under the ROC curve. Model calibration was estimated using the Hosmer-Lemeshow (HL) goodness-of-fit statistic (higher P values imply that the model fit the observed data better).
4. What are the percentages of the bilateral internal thoracic artery used in each group? What method did the authors use? (pedicle or skeletonized?): we were used bilateral internal thoracic artery with pedicle method in about 0.5% of patients in non SWI group . Double internal thoracic arteries were used in none of the SWI cases.
5. Do the authors have any midterm or long-term survival data? It is known from the literature that DSWI affects also long-term mortality in CABG patients. In our study early follow-up (in-hospital follow-up) was simple and after that time patients came to follow-up clinic every 6 months. Among these patients SWI patients referred to clinic of surgery.
6. Did the authors use any risk stratification system (i.e. EuroSCORE or STS)? Was there any correlation with the risk stratification system? Not routinely
7. We corrected references 1, 3, 4, 6, 7, 12 as follow:
sincerely yours
A.Salehiomran